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AN IMPLANT AND A METHOD FOR TREATING AN IMPLANT SURFACETechnical field

The invention relates to an implant for implantation into bone tissue, and to a method for treating an implant surface intended for implantation into bone tissue to improve the biocompatibility of an implant comprising said surface.

Background of the invention

A one-stage procedure is nowadays, in most cases, used for implanting orthopaedic or dental implants, generally metallic implants, into bone tissue.

In the one-stage procedure, a first implant part, such as a dental fixture, is surgically placed into the bone tissue, and a healing cap or a secondary implant part, such as an abutment, is then attached to the first implant part directly after the surgical operation. The soft tissue is thereafter allowed to heal around the healing cap or the secondary implant part. When a healing cap is used, the cap is removed after a few weeks or months without any surgical procedure, and secondary implant parts, such as an abutment and a provisional crown, are attached to the first implant part. The one-stage procedure is for instance described in L Cooper et al: "A multicenter 12-month evaluation of single-tooth implants restored 3 weeks after 1-stage surgery", The International Journal of Oral & Maxillofacial Implants, Vol 16, No 2 (2001).

The two-stage procedure, which in some dental cases still might be necessary to use, involves in a first stage surgically placing a first implant part, such as a dental fixture, into the bone tissue, where it is then allowed to rest unloaded and immobile for a healing period of three months or more in order to allow the bone tissue to grow onto the implant surface to permit the implant to be well attached to the bone tissue, the cut in

the soft tissue covering the implant site being allowed to heal over the implant, and in a second stage opening the soft tissue covering the implant and attaching secondary implant parts, such as a dental abutment and/or a restoration tooth, to the first implant part, such as said fixture, forming the final implant structure. This procedure is for instance described by Brånemark et al: "Osseointegrated Implants in the Treatment of the Edentulous Jaw, Experience from a 10-year period", Almquist & Wiksell International, Stockholm, Sweden.

However, the fact that the implant not should be loaded during the healing period means that the secondary implant parts may not be attached to the first implant part and/or used during the healing period of three months or more. In view of the discomfort associated with this, it is desirable to minimize the time period necessary for the above-mentioned first stage or even perform the entire implantation procedure in a single operation, i.e. to use the one-stage procedure.

For some patients, it might be considered better to wait at least three months before functionally loading the implant, both for one- and two-stage procedures. However, an alternative using the one-stage procedure is to put the implant in function directly after implantation (immediate loading) or a few weeks after implantation (early loading). These procedures are, for instance, described by D M Esposito, pp 836-837, in Titanium in Medicine, Material Science, Surface Science, Engineering, Biological Responses and Medical Application, Springer-Verlag (2001).

It is essential that the implant establish a sufficient stability and bond between implant and bone tissue to enable the above disclosed immediate or early loading of the implant.

It shall also be noted that an immediate or early loading of the implant may be beneficial to bone formation.

Some of the metals or alloys, such as titanium, zirconium, hafnium, tantalum, niobium, or alloys thereof, that are used for bone implants are capable of forming a relatively strong bond with the bone tissue, a bond which
5 may be as strong as the bone tissue per se, sometimes even stronger. The most notable example of this kind of metallic implant material is titanium and alloys of titanium whose properties in this respect have been known since about 1950. This bond between the metal and the
10 bone tissue has been termed "osseointegration" by Bråne-mark et al.

Although the bond between the metal, e.g. titanium, and the bone tissue may be comparatively strong, it is desirable to enhance this bond.

15 There are to date several methods for treating metallic implants in order to obtain a better attachment of the implant, and thus improved osseointegration. Some of these involve altering the morphology of the implant, for example by creating relatively large irregularities on
20 the implant surface in order to increase the surface roughness in comparison to an untreated surface. An increased surface roughness gives a larger contact and attachment area between the implant and the bone tissue, whereby a better mechanical retention and strength may be
25 obtained. A surface roughness may be provided by, for example, plasma spraying, blasting or etching.

Rough etching of implant surfaces may be performed with reducing acids, such as hydrofluoric acid (HF) or mixtures of hydrochloric acid (HCl) and sulfuric acid
30 (H₂SO₄). The aim of such a rough etching process is to obtain implant surfaces with rather large irregularities, such as pore diameters within the range of 2-10 µm and pore depths within the range of 1-5 µm.

Other methods for obtaining a better attachment of
35 the implant to the bone tissue involve alteration of the chemical properties of the implant surface. For example, one such method involves the application of a layer of

ceramic material, such as hydroxyapatite, to the implant surface, inter alia in order to stimulate the regeneration of the bone tissue. Ceramic coatings, however, may be brittle and may flake or break off from the implant surface, which may in turn lead to an ultimate failure of the implant.

Besides the above disclosed methods of implant surface modification, it shall be noted that in contact with oxygen, titanium, zirconium, hafnium, tantalum, niobium and their alloys are instantaneously covered with a thin oxide layer. The oxide layers of titanium implants mainly consist of titanium(IV)dioxide (TiO_2) with minor amounts of Ti_2O_3 and TiO . The titanium oxide generally has a thickness of about 4-8 nm. However, titanium implants having an oxide layer thickness of up to about 20 μm may be produced using anodisation (anodic oxidation). As the titanium oxide layer thickness increases, the porosity and surface roughness of the oxide layer increases. Furthermore, the crystallinity of the titanium oxide increases as the oxide layer thickness increases. Thus, an implant surface roughness may also be obtained by providing a thicker oxide layer.

Our prior application WO 95/17217 describes a process wherein a metallic implant (blasted or non-blasted) is treated with a 0.2% solution of hydrofluoric acid for a treatment period of preferably 30 s at room temperature. According to WO 95/17217, the implant surface morphology is unaffected by this treatment, i.e. no significant etching of the surface occurs.

Our prior application WO 94/13334 describes a process wherein a metallic implant is treated with an aqueous solution containing sodium fluoride having a concentration of about 0.1-4%, pH 2.5-6, for a period of from at least 10 s to about 5 minutes at room temperature.

Both these prior applications describe metallic implants having improved biocompatibility, and methods for production thereof. Specifically, the rate of bone tissue

attachment is increased and a stronger bonding between the implant and the bone tissue is obtained. The improved biocompatibility of these implants is believed to be due to retaining of fluorine and/or fluoride on the implant surfaces.

Fluorine and/or fluoride is, according to J E Ellingsen, "Pre-treatment of titanium implants with fluoride improves their retention in bone", Journal of Material Science: Materials in Medicine, 6 (1995), pp 749-753, assumed to react with the surface titanium oxide layer and replace titanium bound oxygen to form a titanium fluoride compound. In vivo, the oxygen of phosphate in tissue fluid may replace the fluoride in the oxide layer and the phosphate will then become covalently bound to the titanium surface. This may induce a bone formation where phosphate in the bone is bound to the titanium implant. Moreover, the released fluoride may catalyse this reaction and induce formation of fluoridated hydroxyapatite and fluorapatite in the surrounding bone.

Disclosure of the invention

An object of the present invention is to provide an implant for implantation into bone tissue having an improved rate of attachment between the implant and the bone tissue such that the post-surgery healing period described above (either using a one- or two-stage procedure) is reduced and/or an immediate or early loading of the implant is enabled.

Another object of the invention is to provide an implant forming a mechanically stronger bond with bone tissue. Thus, an implant intended for implantation into bone tissue having an improved biocompatibility is to be provided.

Still another object of the invention is to provide a method for treating an implant surface intended for implantation into bone tissue, such as an orthopaedic or dental implant surface, whereby an implant according to the invention is obtained.

According to a first aspect of the invention, these and other objects are achieved with a method for treating an implant surface intended for implantation into bone tissue, which comprises providing fluorine and/or fluoride on at least a part of the implant surface, such as 1-99 area%, preferably > 10 area%, more preferably > 40 area%, with an atomic average concentration of preferably at least 0.2 at%, and providing, on the implant surface, a microroughness having a root-mean-square roughness (R_q and/or S_q) of ≤ 250 nm, such as from 1 nm to 250 nm.

The microroughness comprises surface irregularities in the form of pores, and optionally peaks, and may consequently also be expressed in terms of pore sizes.

Thus, according to a second aspect of the invention, said objects and other objects are achieved with a method for treating an implant surface intended for implantation into bone tissue, which comprises providing fluorine and/or fluoride on at least a part of the implant surface, such as 1-99 area%, preferably > 10 area%, more preferably > 40 area%, with an atomic average concentration of preferably at least 0.2 at%, and providing, on the implant surface, a microroughness comprising pores having a pore diameter of ≤ 1 μ m, such as from 1 nm to 1 μ m, preferably within the range of 50 nm to 1 μ m, and a pore depth of ≤ 500 nm, such as from 1 nm to 500 nm, preferably within the range of from 50 to 500 nm.

Said procedures of the methods according to the invention may be performed in any order or simultaneously.

An embodiment of the method according to the invention comprises treating a metallic implant surface with an aqueous solution of hydrofluoric acid having a concentration of preferably less than 0.5 M, more preferably 0.1 M, resulting in etching, for an etching period of preferably up to 180 sec, more preferably up to 60 sec, at room temperature ($24 \pm 1^\circ\text{C}$). In this embodiment fluo-

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rine and/or fluoride, and a microroughness are provided simultaneously.

It has been shown that surprisingly good biocompatibility results are obtained for an implant, implanted
5 into bone tissue, having an implant surface comprising fluorine and/or fluoride, and a fine microroughness as specified above. Both an improved rate of attachment, and a stronger bond between the implant surface and the bone tissue are obtained. Thus, the fine microroughness in
10 combination with fluorine and/or fluoride improve the osseointegration process.

According to a third aspect of the invention, said objects and other objects are achieved with an implant for implantation into bone tissue having an implant sur-
15 face at least part of which, such as 1-99 area%, preferably > 10 area%, more preferably > 40 area%, has been treated with the method according to the invention as described herein above.

According to a fourth aspect of the invention said
20 objects and other objects are achieved with an implant for implantation into bone tissue having an implant surface, wherein at least a part of the implant surface, such as 1-99 area%, preferably > 10 area%, more preferably > 40 area%, comprises fluorine and/or fluoride, and a
25 microroughness having a root-mean-square roughness (R_q and/or S_q) of ≤ 250 nm, such as from 1 nm to 250 nm.

According to a fifth aspect of the invention said objects and other objects are achieved with an implant for implantation into bone tissue having an implant sur-
30 face, wherein at least a part of the implant surface, such as 1-99 area%, preferably > 10 area%, more preferably > 40 area%, comprises fluorine and/or fluoride, and a microroughness which comprises pores having a pore diameter of ≤ 1 μ m, such as from 1 nm to 1 μ m, preferably
35 within the range of 50 nm to 1 μ m, and a pore depth of ≤ 500 nm, such as from 1 nm to 500 nm, preferably within the range of from 50 to 500 nm.

Other features and advantages of the present invention will become apparent from the embodiments described hereinafter and the appended claims.

Brief description of the drawings

5 Figure 1 defines the terms "pore diameter" (D), "pore depth" (h) and "peak width at half the pore depth" (x).

Figure 2 shows SEM pictures of a coarse-blasted reference implant surface.

10 Fig 3 shows SEM pictures of the herein described and analysed prior art implant surface according to WO 95/17217. The implant surface is non-blasted.

15 Fig 4 shows SEM pictures of an embodiment of the implant surface according to the present invention. The implant surface is non-blasted and has been treated according to method I (Example 1, non-blasted).

20 Fig 5 shows SEM pictures of an embodiment of the implant surface according to the present invention. The implant surface has been coarse-blasted and treated according to method I (Example 1, coarse-blasted).

Fig 6 shows SEM pictures of an embodiment of the implant surface according to the present invention. The implant surface is non-blasted and has been treated according to method II (Example 2, non-blasted).

25 Fig 7 shows SEM pictures of an embodiment of the implant surface according to the present invention. The implant surface has been coarse-blasted and treated according to method II (Example 2, coarse-blasted).

30 Fig 8 illustrates the AFM profile of the surface shown in Fig 3 (prior art implant).

Fig 9 illustrates the AFM profile of the surface shown in Fig 4 (Example 1, non-blasted).

Fig 10 illustrates the AFM profile of the surface shown in Fig 6 (Example 2, non-blasted).

35 Figure 11 illustrates the distribution of fluorine and/or fluoride (measured using TOF-SIMS) on the implant

surface of the surface shown in Fig 5 (Example 1, coarse-blasted).

Figure 12 illustrates the distribution of fluorine and/or fluoride (measured using TOF-SIMS) on the implant surface of the surface shown in Fig 7 (Example 2, coarse-blasted).

Detailed description of the invention

As used herein in connection with the invention the term "etching" refers to the process taking place during the treatment period during which H₂ (g) is generated at the implant surface. The etching period is measured from the formation of the first bubble of H₂(g) at the implant surface. Etching in the context of the present invention relates to a very mild etching of an implant surface providing the desired microroughness described herein.

As used herein the term "microroughness" refers to a surface roughness comprising pores having a pore diameter equal to or less than 1 µm and a pore depth equal to or less than 1 µm.

As used herein the term "macroroughness" refers to a surface roughness comprising surface irregularities having dimensions greater than 1 µm.

As used herein the term "implant" includes within its scope any device intended to be implanted into the body of a vertebrate animal, in particular a mammal, such as a human. Implants may be used to replace anatomy and/or restore any function of the body.

Generally, an implant is composed of one or several implant parts. For instance, a dental implant usually comprises a dental fixture coupled to secondary implant parts, such as an abutment and/or a restoration tooth. However, any device, such as a dental fixture, intended for implantation may alone be referred to as an implant even if other parts are to be connected thereto.

As used herein the term "implant (intended) for implantation into bone tissue" refers to implants intended for at least partial implantation into bone tissue, such

as dental implants, orthopaedic implants, and the like. An implant for implantation into bone tissue may also be referred to as a bone tissue implant.

As used herein the term "implant surface" refers to
5 at least one defined surface region of an implant. Thus, the defined surface region may include the entire surface area of the implant or portions thereof.

An example of an implant surface intended for im-
plantation into bone tissue is the surface of a dental
10 fixture that is intended for implantation into the jaw-bone of a patient and to be in contact with bone tissue.

Another example of an implant surface intended for
implantation into bone tissue is the surface of a hip
joint implant that is intended for implantation into the
15 neck of the femur of a patient.

The terms "pore diameter" (D), "pore depth" (h) and
"peak width at half the pore depth" (x) are defined in
Fig 1. These terms are used in the context of a micro-
roughness. In Fig 1, a microroughness is superimposed on
20 a macroroughness. However, the same terms are used for a
microroughness provided on a surface lacking said
macroroughness.

The pore diameter (D) is the distance between the
highest points of two adjacent peaks as defined in Fig 1.
25 If there are several points at the same level that could
be referred to as the highest, the point closest to the
pore should be chosen. If the "peaks" are very broad
(i.e. the surface might seem to lack well-defined peaks),
the surface may be described as having an essentially
30 flat surface profile in-between the pores (forming said
microroughness), which are spread over the surface. In
that case, the pore diameter is the distance between
those points where the surface profile start to deviate
from the essentially flat surface profile, thus forming
35 said pore. This is in compliance with said definition
shown in Fig 1.

The pore depth (h) is defined as the distance between an imaginary line drawn between the highest points of two adjacent peaks, and the bottom of the pore (at the lowest point) (see Fig 1). The distance is measured in a direction perpendicular to the tangent of said lowest point of the pore. If there are several points at the lowest level, a mean value of the distances from these points to the imaginary line is calculated as the pore depth. If no well-defined peaks are present, the imaginary line is drawn between those points where the surface profile start to deviate from an essentially flat surface profile, thus forming said pore.

The peak width (x) at half the pore depth (h) is defined as shown in Fig 1.

The present invention relates to a method for treating an implant surface intended for implantation into bone tissue, which comprises providing fluorine and/or fluoride on at least a part of the implant surface, and providing, on the implant surface, a microroughness having a root-mean-square roughness (R_q and/or S_q) of ≤ 250 nm. The root-mean-square roughness corresponds to the root-mean-square deviation of the profile from the mean line over one sampling length. R_q is the root-mean-square roughness measured in two dimensions and S_q is the root-mean-square roughness measured in three dimensions.

The root-mean-square roughness (R_q and/or S_q) may be measured with atomic force microscopy (AFM) for a surface area of $5 \times 5 \mu\text{m}$. AFM is a very sensitive method of surface characterisation. However, the analysis must be carefully executed so that the microroughness is analysed and not the underlying surface structure, such as a blasted or machined surface.

The root-mean-square roughness may also be calculated based upon the surface morphology shown on SEM pictures of the implant surface or estimated from results obtained by any other method of surface characterisation.

Thus, calculations using a pore diameter of $\leq 1 \mu\text{m}$ and a pore depth of $\leq 500 \text{ nm}$ gives a root-mean-square roughness (R_q) of $\leq 250 \text{ nm}$ based upon the definition of root-mean-square roughness (R_q) as is known to persons skilled in the art.

The microroughness, which comprises surface irregularities in the form of pores, and optionally peaks, may also be expressed in terms of pore sizes.

Thus, a method, according to the invention, for treating an implant surface intended for implantation into bone tissue comprises providing fluorine and/or fluoride on at least a part of the implant surface, and providing a microroughness comprising pores having a pore diameter of $\leq 1 \mu\text{m}$, preferably within the range of 50 nm to $1 \mu\text{m}$, and a pore depth of $\leq 500 \text{ nm}$, preferably within the range of 50 to 500 nm , on the implant surface.

Furthermore, the microroughness may also preferably comprise peaks having a peak width, at half the pore depth, of from 15 to 150% of the pore diameter (see Fig 1). Thus, the peak width is preferably within the range of 7.5 nm to $1.5 \mu\text{m}$. Even more preferably are peaks having a peak width, at half the pore depth, of from 30 to 150% of the pore diameter. Most preferably are peaks having a peak width, at half the pore depth, of from 60 to 150% of the pore diameter.

This specific surface morphology gives a very resistant bone in-growth. With this specific morphology, newly formed bone, which grows into the surface irregularities of the implant surface, does not easily fracture from the old bone. In addition, the peaks of the implant surface do not easily fracture from the implant.

Furthermore, it shall be noted that only a part or parts of the implant surface may comprise the herein specified surface irregularities, which means that pores, and optionally also peaks, may be grouped in several regions throughout the surface. Thus, the distances between pores and/or peaks may vary throughout the surface. Pref-

erably, > 10 area% of the implant surface comprises said surface irregularities, more preferably > 40 area%, and still more preferably ≥ 70 area%. Most preferably, the entire implant surface comprises said surface irregularities homogeneously distributed throughout the surface.

It is not necessary that said at least a part of the implant surface comprising fluorine and/or fluoride overlaps with said part or parts of the implant surface comprising surface irregularities. There may be surface areas, including spots, having only surface irregularities and areas having only fluorine and/or fluoride. However, at least partial overlap of surface irregularities and fluorine and/or fluoride is preferred.

The root-mean-square roughness (R_q and/or S_q), estimated as disclosed above, of the microroughness having the pore sizes given above is preferably ≤ 250 nm.

Consequently, the method for treating an implant surface intended for implantation into bone tissue according to said first and second aspect of the invention may also be expressed as comprising:

providing fluorine and/or fluoride on at least a part of the implant surface, and

providing, on the implant surface, a microroughness having a root-mean-square roughness (R_q and/or S_q) of ≤ 250 nm and/or comprising pores having a pore diameter of ≤ 1 μm and a pore depth of ≤ 500 nm.

Preferably, the implant surface has an average atomic concentration of at least 0.2 at% fluorine and/or fluoride measured with X-ray photoelectron spectroscopy (XPS) for a surface area of 100×100 μm .

The average atomic concentration of fluorine and/or fluoride is advantageously ≤ 20 at% measured with XPS.

Most preferably, the average atomic concentration of fluorine and/or fluoride is within the range 0.4-7 at% measured according to above. However, the initially provided amount of fluorine and/or fluoride might need to

be higher due to potential decrease during storage of the implant.

The implant surface is preferably a metallic implant surface, such as a titanium implant surface.

5 The metallic implant surface might be part of a metallic implant or it might be an applied metallic surface layer of a non-metallic implant, such as a ceramic, a plastic or a composite material. Furthermore, the metallic implant surface might also be part of a partly metallic implant, whereby a partly metallic implant surface is provided.

10 The fluorine and/or fluoride is/are preferably incorporated within the oxide layer on the metallic implant surface providing an oxide layer which is more reactive than an oxide layer without fluorine and/or fluoride (see the Examples). A titanium oxide with incorporated fluorine and/or fluoride has a disturbed oxide structure as compared to an ordinary pure titanium oxide structure. Without being bound by any theory, the disturbed oxide structure gives a more reactive oxide layer, which means that the oxide in vivo probably to a higher degree, as compared to a pure titanium oxide structure, interacts with molecules, such as phosphate ions, and probably also grows at a higher rate, which means that an improved bio-

15 compatibility is attained.

20 The fluorine and/or fluoride can be provided on the implant surface using any suitable method, such as:

- plasma deposition using a plasma comprising fluorine and/or fluoride, e.g. a CHF_3 -plasma,
- 30 - any electrochemical treatment involving fluorine and/or fluoride, e.g. anodisation in an electrolyte comprising fluoride and/or fluorine,
- treatment with an aqueous and/or non-aqueous solution comprising fluorine and/or fluoride, e.g. solutions comprising dissolved fluoride salts, such as NaF, or
- 35 HF(aq),
- ion implantation, or

- any combination of these methods or the like..

Before, after or simultaneous with the provision of the fluorine and/or fluoride, a microroughness may be provided using mild etching, micro fabrication, anodisation, flame spraying, electrochemical treatment, laser, spark erosion, or any other suitable method of surface modification.

Preferably, the fluorine and/or fluoride and the microroughness is provided simultaneously by treating the metallic implant surface with an aqueous solution of hydrofluoric acid (HF), resulting in an etching process.

The concentration of the hydrofluoric acid is preferably less than 0.5 M, more preferably 0.1 M.

The metallic implant surface is preferably treated for an etching period of up to 180 sec, more preferably up to 60 sec, at room temperature ($24 \pm 1^\circ\text{C}$). Before the etching starts the natural oxide layer is removed by the acid and when the acid gets in contact with the implant surface, the etching process starts. A new oxide layer with fluorine and/or fluoride incorporated therein and distributed throughout the oxide layer is then formed. Furthermore, the above disclosed microroughness is provided by the etching process of the implant surface.

It shall be noted that even if treatment with hydrofluoric acid is used both for providing fluorine and/or fluoride and a microroughness on the implant surface, these procedures may be performed separately and in inverted order.

The treatment with HF(aq) is preferably performed at room temperature, i.e. at about $20-30^\circ\text{C}$ (normal air pressure), preferably $24 \pm 1^\circ\text{C}$. If a higher temperature than $24 \pm 1^\circ\text{C}$ is used, the etching process will, as known to a person skilled in the art, be initiated earlier and the etching process will be more rapid, i.e. a shorter etching period than the period given herein for etching at $24 \pm 1^\circ\text{C}$ is needed to obtain the desired result. Hence, if a lower temperature than $24 \pm 1^\circ\text{C}$ is used, a longer etching

period than the period given herein for etching at $24 \pm 1^\circ\text{C}$ is needed to obtain the desired result.

The etching period, the temperature and the concentration of HF (aq) determines the ratio between etched
5 areas, i.e. areas having a microroughness, and non-etched areas.

Rinsing removes any loosely adhered fluorine and/or fluoride and impurities from the implant surface. Thus, an implant having a better shelf life is then obtained.
10 Thus, the implant surface is preferably rinsed after the provision of fluorine and/or fluoride thereon.

Preferably, the method further comprises providing a macroroughness on the implant surface prior to providing the fluorine and/or fluoride and prior to providing the
15 microroughness. Thus, an implant having a microroughness superimposed on the macroroughness is obtained. The macroroughness is preferably provided by blasting, more preferably blasting a titanium implant surface with titanium dioxide particles.

20 A macroroughness may also be provided by any other suitable technique, such as etching, micro fabrication, anodisation, flame spraying, any electrochemical treatment, laser, spark erosion, machining, knurling, or any other suitable method of surface modification.

25 Furthermore, it shall also be noted that the implant surface, with or without a macroroughness, may be either unthreaded or threaded.

Said metallic implant surface is preferably made of commercially pure titanium or an alloy of titanium, but
30 it may also be made of any other biocompatible metallic material, such as zirconium or an alloy thereof, hafnium or an alloy thereof, niobium or an alloy thereof, tantalum or an alloy thereof, a chromium-vanadium alloy, or any combination of these materials.

35 The implant for implantation into bone tissue according to the invention is preferably a dental implant or an orthopaedic implant.

The present invention also relates to an implant for implantation into bone tissue having an implant surface at least part of which has been treated with the method according to the invention as described herein above.

5 Thus, an implant for implantation into bone tissue having an implant surface with the above described characteristics also forms part of the present invention.

The invention will now be illustrated by means of the following non-limiting examples.

10 EXAMPLES

Sample preparation

Surgical implants of commercially pure (c.p.) titanium were used.

Each implant was ultrasonically degreased in
15 Ecosolv[®] (70-100% ethyl-2-hydroxypropionate) for 5 min, and thereafter in ethanol (70%) for 5 min.

Some of the implants were thereafter blasted with titanium dioxide particles. Two different particle size ranges of titanium dioxide were used; 6.8-90 μm (fine =
20 F), and 106-180 μm (coarse = C). However, coarser particles sizes, such as 180-300 μm , may also be used.

The blasted implants were then ultrasonically rinsed in deionised water for 2 x 5 min, and in ethanol for 2 x 5 min to remove any residual blasting particles.

25 The implants were then treated according to the following methods:

a) Reference implants

Non-blasted and blasted (F and C) implants, cleaned in accordance with above, were provided as references for
30 the studies as described hereinafter.

b) Prior art method (according to WO 95/17217)

Non-blasted and blasted implants (F and C), cleaned in accordance with above, were immersed in 0.1 M HF (aq) at room temperature (about $24 \pm 1^\circ\text{C}$) for 90 s. No $\text{H}_2(\text{g})$
35 was formed during this treatment period, thus no etching occurred.

The implants were thereafter immersed in deionised water for 20 s, and thereafter dried.

c) *Method I*

Non-blasted and blasted implants (F and C), cleaned
5 in accordance with above were immersed in ethanol (99.5% for 2 s and in deionised water for 5 s.

The implants were thereafter, according to the present invention, immersed in a stirred solution of 0.1 M HF (aq) at room temperature (about $24 \pm 1^\circ\text{C}$) for an etching
10 ing period of 40 ± 5 sec. About 80-90 area% of the surface was then etched, thus providing a microroughness. However, since the etching process was shown to be slower for non-blasted implants, these implants should preferably be etched for a longer time period, such as 60 ± 5
15 sec, than blasted implants to obtain a similar degree of etching. The etching period was measured from the formation of the first bubble of $\text{H}_2(\text{g})$ at the implant surface. The etching of the implant surface starts when the acid is in direct contact with the pure titanium, i.e. when
20 the titanium oxide covering the titanium surface is removed.

The implants were thereafter immersed in stirred deionised water for 20 s.

The implants were ultrasonically rinsed in ethanol
25 (20%) for 3 min, and in deionised water for 4 min.

The implants were then rinsed in ethanol (99.5%) for 5 s, wiped, and dried.

An implant treated in accordance with this method is referred to as Example 1.

30 d) *Method II*

Non-blasted and blasted (F and C) implants, cleaned in accordance with above, were immersed in ethanol (99.5%) for 2 s and in deionised water for 5 s.

The implants were thereafter, according to the present invention, immersed in 0.1 M HF (aq) at room temperature (about $24 \pm 1^\circ\text{C}$) with stirring for an etching
35 period of 40 ± 5 sec. Due to reasons explained above,

some of the non-blasted implants were etched for 60 ± 5 sec (these samples were only used for the AFM measurement described hereinafter). The etching period was measured from the formation of the first bubble of $H_2(g)$ at the
5 implant surface.

The implants were then wiped and dried.

An implant treated in accordance with this method is referred to as Example 2.

In vivo evaluation

10 Implant surfaces treated in accordance with the above methods were evaluated in vivo using the tensile test described in Biomaterials 23 (2002), pp 2201-2209, by H J, Ronald, and J E Ellingsen.

The implants were in the form of coins having a di-
15 ameter of 6.25 mm and a height of 1.95 mm. One side of the implant coins were treated with said methods. In the centre of the other side of the coin, a threaded hole for attachment to a load cell was provided.

New Zealand white rabbits were used as test animals.
20 Two guide holes were drilled in one of each rabbit's tibial bone using a 1.0 mm diameter twist drill (Medicon[®], Germany) using a drill guide to ensure a standardised and correct positioning. Cavities were then prepared for each implant coin using a custom made 7.05 mm diame-
25 ter stainless steel bur mounted in a slow speed dental implant drill with copious physiological saline solution irrigation.

The treated and untreated implant surfaces, according to Table 1, were placed in the cavities and stabilised by a pre-shaped 0.2 mm titanium maxillofacial plate
30 (Medicon[®] CMS, Germany), retained in the cortical bone by two 1.2 x 3 mm² titanium screws (Medicon[®] CMS, Germany). This ensured a stable passive fixation of the implants during the healing period. Polytetrafluorethylene (PTFE)
35 caps were introduced to resist bone growth towards the vertical faces of the implant as well as bone overgrowth.

The subcutaneous soft tissue and the superficial layers were repositioned and sutured.

The treated surface was in direct contact with the bone tissue, but the vertical sides and the reverse side
5 of the coin were not in contact with bone tissue.

The implant coins were then left for 7 weeks in test 1, and for 8 weeks in test 2.

18 rabbits were used in test 1, and 20 rabbits were used in test 2.

10 At the end of said period, the rabbits were sacrificed, and the implant fixations and the PTFE caps were removed. The tibial bone was then fixed in a specially designed rig to stabilise the bone during the test procedure. A threaded pin with a ball-head was attached to the
15 implant coin by use of the pre-made threaded hole and the set-up was adjusted perpendicularly to the load cell using a level tube. Tensile tests were then performed using a Lloyds LRX Materials testing machine fitted with a calibrated load cell of 100 N. Cross-head speed range was
20 set to 1.0 mm/min. Load was applied until the implant detached from the bone and the force applied was recorded on a load versus displacement plot. The detachment of the implant coin was in this plot indicated as a well-defined breakpoint with a vertical drop in load. The mean values
25 of the forces needed to pull out the differently treated coins are given in Table 1. The recorded force gives a direct assessment of the strength of connection between the implant coin and the bone. The higher the recorded force, the stronger the connection.

30 The first test included a reference coin blasted with fine (F) titanium dioxide particles, and blasted (F) coins treated in accordance with the prior art method, method I, and method II as outlined above.

The second test included a reference coin blasted
35 with fine (F) titanium dioxide particles, a reference coin blasted with coarse (C) titanium oxide particles,

and blasted (C) coins treated in accordance with method I and method II as outlined above.

Table 1

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	Reference implant		Prior art implant		Example 1		Example 2	
Blasting particles	F	C	F	-	F	C	F	C
Test 1: Recorded force [N]	18.3	-	20.1	-	29.0	-	26.2	-
Test 2: Recorded force [N]	17.1	32.2	-	-	-	39.8	-	38.2

As can be seen from Table 1, the implant coins treated in accordance with method I and II gave an improved bone attachment as compared to the reference coins and the coins treated according to the prior art method.

Furthermore, it shall be noted that the coin implants blasted with coarse (C) titanium oxide particles gave a better bone attachment than coin implants blasted with fine (F) titanium oxide particles.

15 Surface characterisation

The surface characteristics of implants treated in accordance with the methods disclosed above were evaluated using X-ray Photoelectron Spectroscopy (XPS), Atomic Force Microscopy (AFM), Scanning Electron Microscopy (SEM), and Time-of-Flight Secondary Ion Mass Spectrometry (TOF-SIMS). Surface roughness, average atomic concentration of fluorine and/or fluoride, and distribution of fluorine and/or fluoride on the implant surface and throughout the oxide layer were evaluated.

25 XPS (Quantum 2000 ESCA Scanning Microscope, Physical Electronics, USA) was used to measure the average atomic concentration of fluorine and/or fluoride over an area of

100 x 100 μm . Monocromated AlK α was used as X-ray source and a pass energy of 187.8 eV was utilised.

TOF-SIMS (TRIFT II Time-of-Flight SIMS, Physical Electronics, USA) was used to evaluate the surface distribution (x- and y-direction) of fluorine and/or fluoride over an area of 250 x 250 μm (see Fig 11 and Fig 12). The primary ion beam energy was 25 kV and $^{69}\text{Ga}^+$ was used as primary ion beam.

Angle XPS (Quantum 2000 ESCA Scanning Microscope, Physical Electronics, USA) and argon sputtering was used to evaluate the depth distribution (z-direction) of fluorine and/or fluoride within the oxide layer.

AFM (AFM DualScope, DME AS, Denmark) was used to measure the morphology of the implant surfaces. Two sizes of sample areas were measured, 5 x 5 μm (256 points sampling in x- and y-direction) and 10 x 10 μm (256 points sampling in x- and y-direction), respectively (see Fig 8-10). The z-scaling of the 3D-pictures (5 x 5 μm) shown in Fig 8-10 has been increased four times.

SEM (Philips XL-30 ESEM, Philips, the Netherlands) was used to visually study the surface morphology (see Fig 2-7).

The average atomic concentrations and the surface distribution of fluorine and/or fluoride for the implant coins used in the in vivo study are given in Table 2.

The implant treated according to WO 95/17217 had an atomic average concentration of about 1.1 at% fluorine and/or fluoride.

The implant treated with method I and method II, respectively, according to the present invention had an atomic average concentration of about 0.8 and 5-6 at% fluorine and/or fluoride, respectively. The halogen atoms provided are most likely, and preferably, mainly fluoride.

The ultrasonic rinsing removes loosely adhered fluorine and/or fluoride from the implant surface and the atomic average concentration of fluorine and/or fluoride

is decreased. Furthermore, a heterogeneous distribution of fluorine and/or fluoride is obtained. The TOF-SIMS pictures of the coarse-blasted (C) surfaces of Example 1 and Example 2 are shown in Fig 11 and Fig 12, respectively. In these figures red indicates F^- , blue indicates O^- , and where F^- and O^- overlap in equal amounts magenta results. The scale mark corresponds to 100 μm . The surface distribution of F^- is in Fig 11 shown to be rather heterogeneous for Example 1. Fig 12 shows a rather homogeneous distribution of F^- for Example 2.

Table 2

	Reference implant		Prior art implant		Example 1		Example 2	
	F	C	F	-	F	C	F	C
Blasting particles								
Average fluorine/fluoride conc. [at%]	-	-	1.1	-	0.8	0.8	5.1	6.2
Surface area with fluorine/fluoride [%]	-		~60-70		~40-50		~100	

Non-blasted implants treated according to method I and II (an etching period of 40 ± 5 sec) were evaluated with regard to distribution of fluorine and/or fluoride throughout the titanium oxide layer.

The average atomic concentrations of fluorine and/or fluoride for Example 1 and Example 2 used in this analysis were 0.5 at% and 5 at%, respectively.

The non-blasted implant treated according to method II (Example 2) was studied using sputtering with argon.

These results are given in Table 3. It can be seen in Table 3 that the oxide layer has a decreasing concentration of fluorine and/or fluoride from the surface and downwards.

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Table 3

Oxide layer depth [nm]	Example 2 [at%]
0.75-1.25	3.9
1.65-2.75	3.2
3.30-5.50	3.1
4.65-7.75	2.3
5.70-9.50	2.1
6.45-10.75	2.0

However, argon sputtering was not suitable for the analysis of Example 1 since the atomic concentration was too low for such an analysis. Thus, this implant surface was analysed using XPS with different take-off angles (10-90°). These results are given in Table 4. It can be seen in Table 4 that the fluorine and/or fluoride is evenly distributed in the oxide layer to a depth of at least about 7 nm.

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Table 4

Take-off angle	Oxide layer depth [nm]	Example 1 [at%]
10°	1.15	0.4
15°	1.71	0.4
20°	2.26	0.5
30°	3.30	0.4
45°	4.67	0.4
60°	5.72	0.6
90°	6.60	0.5

Furthermore, the surface characteristics for implants treated in accordance with the methods disclosed

20

above were evaluated. Non-blasted implants and implants blasted with coarse (C) titanium dioxide particles were studied.

The implant surfaces were studied by SEM and AFM.

5 SEM pictures of an untreated, coarse-blasted (C) reference implant surface are shown in Fig 2 (magnification x500, and x10 000).

SEM pictures of the non-blasted implant surface treated according to the prior art method described above are shown in Fig 3 (magnification x2 500, and x10 000).
10 An AFM graph of this surface is shown in Fig 8.

SEM pictures of the non-blasted and coarse-blasted (C) implant surfaces treated according to method I are shown in Fig 4 (magnification x2 500, and x10 000) and
15 Fig 5 (magnification x60 000 and x120 000), respectively. An AFM graph of the non-blasted surface shown in Fig 4 is shown in Fig 9.

SEM pictures of the non-blasted and coarse-blasted (C) implant surfaces treated according to method II are
20 shown in Fig 6 (magnification x2 500, and x10 000) and Fig 7 (magnification x500, and x10 000), respectively. An AFM graph of the non-blasted surface shown in Fig 6 is shown in Fig 10.

The results indicated that both blasted and non-
25 blasted implants treated according to method I and II had pores with a pore diameter of 100-600 nm, more specifically predominantly around 250-300 nm, a pore depth of 50-300 nm, more specifically predominantly around 60-150 nm, and a peak width, at half the pore depth, of 150-670
30 nm.

The microroughness parameters obtained for the non-blasted surfaces using AFM are given in Table 5. Parameter values for two regions of the implant surface were recorded and these values are given in Table 5.

Table 5

	Reference implant	Prior art implant	Example 1	Example 2
Blasting particles	no blast	no blast	no blast*	no blast**
Measured area: 10 x 10 μm				
S_a [μm]	0.04	0.06	0.13	0.12
	0.04	0.05	0.08	0.10
S_q [μm]	0.04	0.07	0.16	0.14
	0.05	0.07	0.10	0.12
S_{dr} [%]	1.1	1.9	49.3	20.0
	2.0	1.8	40.3	10.7
Measured area: 5 x 5 μm				
S_a [μm]	0.03	0.02	0.10	0.09
	0.04	0.04	0.07	0.09
S_q [μm]	0.03	0.03	0.12	0.11
	0.04	0.05	0.08	0.11
S_{dr} [%]	1.5	1.2	46.8	19.7
	2.4	5.3	35.8	12.2

* Etching period: 40 ± 5 sec

** Etching period: 60 ± 5 sec

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As can be seen in Table 5, the S_a and S_q are about 0.07-0.13 μm and 0.08-0.16 μm , respectively, for the implants of Example 1 and Example 2, which are embodiments of the present invention.

10 Furthermore, the surface developed ratio (S_{dr}), i.e. the increase of surface area as compared to a smooth area, is increased for the implants of Example 1 and Example 2 in comparison to the reference and prior art implant.

15 Moreover, it can be seen from Table 5 that the surface morphology of the implant surface treated according to the prior art method is similar to the reference implant surface, i.e. the surface is unaffected, which is

also confirmed by the SEM pictures (Fig 3). The values obtained (shown in Table 5) are most likely due to machine traces.

To improve the accuracy and to obtain higher resolution of the AFM measurement for blasted surfaces, the AFM scanner was placed in an vibration damping sample stage. A blasted (C) surface treated according to method I was analysed with this modified instrument set-up. These values are given in Table 6.

Table 6

	Example 1
Blasting particles	C
Measured area: 5 x 5 μm	
S_a [μm]	0.19 0.11
S_q [μm]	0.22 0.13
S_{dr} [%]	26.89 50.89

As can be seen in Table 6, the S_a and S_q are about 0.11-0.19 μm and 0.13-0.22 μm , respectively, for the coarse-blasted implant of Example 1.

The SEM pictures (see Fig 4-7) and the AFM results (see Fig 9 and Fig 10) show that the microroughness of blasted and non-blasted surfaces treated according to the method of the present invention, i.e. in this example method I and method II, are almost identical. Furthermore, it can be seen that the implant treated with the prior art method is unaffected, i.e. the surface is almost identical to the untreated reference implant.

Reactivity of the titanium oxide layer

To show that the reactivity of the titanium oxide having incorporated fluorine and/or fluoride increases, the following experiment was performed.

The oxide reactivity of different oxide layers can be estimated from measuring the time period from immersing the implant in diluted HF (aq) and to the formation of the first bubble of H_2 (g) at the implant surface. A concentration of 0.1 M HF (aq) was used in this experiment.

Blasted (C) implants treated according to method II as disclosed above were compared with a blasted (C) reference implant.

Table 7

Implant storage time	Time period to first bubble of H_2 (g) [s]	
	Reference implant	Example 2
1 h		16-17
24 h	40-45	25-27
72 h	45-51	27-28
384 h	56-64	34
720 h	75-79	66-69
1008 h		66-69
1200 h	98-100	
2 months		59-60
2.5 months	85-89	
3.5 months		64
6.5 months		89-95
11 months	107-114	

Table 7 shows that the etching process of the implant surface treated with method II (Example 2) initiate earlier than the untreated reference implant surface.

The time period until formation of the first bubble of H_2 (g) increases with storage time. This is probably due to an increase of the oxide layer thickness upon storage.

However, even after a storage period of about 6.5 months, the etching process of the implant surface

treated with method II initiate earlier than the untreated reference implant surface.

These results may either be interpreted as indicating a thinner initial oxide layer of the implant surface treated with method II as compared to the untreated reference implant surface, or it may be interpreted as indicating a disturbed, hence more reactive, oxide layer of the implant surface treated with method II.

Since the oxide layer thickness of the implant surface treated with method II was measured to be within the normal range of thickness, using sputtering with argon ions, it is more likely that the oxide layer of the implant surface treated with method II is more reactive due to a disturbed oxide structure.

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent for one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.